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| 10/728,291 | 12/04/2003 | Stephen F. Badylak | 3220-73986 | 7088 |

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| EXAMINER | |
|---|---|
| FORD, ALLISON M | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/728,291 | BADYLAK ET AL. | |
| | Examiner | Art Unit | |
| | ALLISON M. FORD | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070320*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response of 3/20/08 has been received and entered into the application file. Claim 1 has been amended; new claims 9-24 have been added.

### *Election/Restrictions*

Newly submitted claims 9-16 will be examined along with original claims 1-8, as they are directed to a related method. However, newly submitted claims 17-24 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

New claims 17-24 are directed to a composition comprising liver basement membrane and functional hepatocytes, such a composition is considered to be related to the method of claims 8-16 as product and process of use. Inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the composition (product) of new claims 17-24 can alternatively be used as a model system for liver for *in vitro* or *ex vivo* testing, such as toxicology and/or drug testing. Use of a composition for *in vitro* or *ex vivo* testing is considered a patentably distinct method from the claimed method of inducing repair of damaged or diseased liver tissue by implantation of a graft formed from the composition, as one method requires implantation into a subject in need thereof, and the other method requires exposure to various testing conditions *in vitro*. Therefore, the composition of claims 17-24 is considered a patentably distinct invention from the methods of claims 8-16.

Since applicant has received an action on the merits for the originally presented invention (a method for inducing repair of damaged or diseased liver tissue in a patient), this invention has been

constructively elected by original presentation for prosecution on the merits. Accordingly, claims 17-24 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

***Status of Claims***

Claims 1-24 remain pending in the current application, of which claims 17-24 are withdrawn from consideration as being directed to a non-elected invention. Claims 1-16 have been considered on the merits.

***Response to Arguments***

Applicants' arguments of 3/20/08 have been fully considered. Each argument will be addressed below as appropriate. Rejections/objections not repeated herein have been withdrawn from consideration.

With regards to the rejection of claims 1-8 under 35 USC 112, first paragraph, the amendments to the claims have obviated the grounds of rejection.

With regards to the rejection of claims 1-8 under 35 USC 112, second paragraph, the amendments to the claims, in combination with the arguments, have obviated the grounds of rejection; however, the amendments have necessitated the new grounds of rejection set forth below.

With regards to the rejection of claims 1-8 as being obvious under 35 USC 103(a) and/or under the provisions of double patenting, Applicants assert that the Examiner has not established a proper *prima facie* case of obviousness, yet even if such a case was made, Applicants assert the rejections are overcome by a showing of unexpected results.

Applicants have not set forth reasons why the rejection of record fails to set forth a proper *prima facie* case of obviousness, thus the comments will be limited to the assertions of unexpected results. Applicants have asserted that the liver basement membrane used in the current method provides the unexpected result of being capable of maintaining functional hepatocytes in culture, whereas the prior art only suggested the liver basement membrane composition could support and stimulate hepatocyte proliferation. Applicants cite Yamamoto et al (Hepatology Research, 2006), Wang et al (World J Gastroenterol, 2004) and Campbell et al (In Vitro Cell Dev Bio Meeting, 2007) to show that the art, even post-filing, recognized difficulties in maintaining physiological functions of hepatocytes *in vitro*. As examples of the maintained functionality of the hepatocytes, Applicants report albumin production of hepatocyte culture on liver basement membrane was superior to hepatocytes cultured on adsorbed collagen. Applicants report the albumin production, urea content and cytochrome P450 activity was comparable to hepatocytes cultured on double-gel substrates.

In response, Applicants' arguments are not found persuasive for two reasons: (1) Applicants are arguing limitations not in the presently examined claims, and (2) there is insufficient evidence provided to show the asserted 'unexpected results' are, in fact, unexpected.

First, it is noted that the current claims are directed to methods of inducing the repair of damaged or diseased liver tissue in a patient; as such the claims are interpreted as encompassing any form of repair, including maintenance of a hepatocyte's ability to produce albumin, process urea, exhibit cytochrome P450 activity, and/or proliferation of hepatocytes. The current claims are not limited to methods whereby hepatocytes exhibiting a specific function (albumin production, urea content, and/or cytochrome P450 activity) are developed, increased, or maintained, but rather are broadly directed to methods of repairing liver tissue. In the absence of a more limiting definition, increasing the liver tissue mass via proliferation of hepatocytes may be considered a reasonable interpretation of 'liver tissue repair'. The fact that the prior

art suggests proliferation and growth of hepatocytes on the liver basement membrane does provide a reasonable expectation of success for repairing liver tissue, in at least some capacity, thereby rendering obvious the invention *as claimed*. Thus, while Applicants may argue that hepatocytes cultured on liver basement membrane produces the unexpected result of maintaining hepatocyte functionality, such is not required by the current claims, and thus is not sufficient to overturn the obviousness rejection. Furthermore, it is pointed out that the particular "functionality" which the hepatocytes are to maintain is not clearly pointed out. Hepatocytes are capable of carrying out numerous cellular functions, without recitation of a specific function as a particular endpoint (in that the cultured cell would exhibit a particular function) even recitation of "maintained functionality" in the claim would be insufficient to define the invention over the prior art.

Second, it is respectfully submitted that Applicants have not provided sufficient evidence that it would have been unexpected for hepatocytes to retain their functionality *in vitro* upon culture on the liver basement membrane. The references cited by Applicants have each been carefully reviewed, but are not found persuasive to support non-obviousness. It is respectfully submitted that the portions of the references on which Applicants rely are limited to discussion of previous difficulties with hepatocyte culture; review of the full teachings of each of the references shows different culture techniques which have been developed to overcome difficulties of losing hepatocytic functions, and each reference reports maintenance of hepatocyte functionality *in vitro*. For example, Yamamoto et al reveal "optimal culture conditions" that *are* capable of maintaining the phenotype of primary hepatocytes in long-term culture, including retention of liver-specific functions and proliferate potential (See Yamamoto et al, abstract, last 2 sentences); Campbell et al report work showing hepatocytes retaining cytochrome p450 activity up to 21 days in culture (See Campbell et al, approximately lines 18-20); Wang et al report hepatocytes cultured in collagen gel mixtures demonstrate superior urea synthesizing ability compared to normally

cultured hepatocytes (See Wang et al, Pg. 702, only paragraph). Furthermore, a review of the evidence cited from the specification fails to show that maintenance of 'functional hepatocytes' was unknown or unexpected, rather Applicants compare their culture method (on liver basement membrane) to the well known double-gel surface culture system. Thus, it is submitted that the double-gel surface culture system was known to result in maintenance of hepatocellular- specific functions, and thus such culture systems were not unheard of, but known in the art. Still further, it is submitted that Applicants are culturing hepatocytes on basement membrane derived from the liver, thus in total, Applicants are merely culturing hepatocytes on their natural substrate. As such, one of ordinary skill in the art would have a reasonable expectation the cells, cultured on the same substrate as found *in vivo*, would exhibit their normal metabolic functions as found *in vivo*; thus maintenance of the hepatocellular-specific functions by culturing the hepatocytes on their natural substrate is not considered to be 'unexpected', but predictable.

As a whole, Applicants' arguments are not found persuasive to demonstrate unexpected results to overturn the obviousness rejections of record. Both the rejections under 35 USC 103(a) and under the provisions of obviousness-type double patenting are therefore maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 1-16 are rejected under 35 U.S.C. 103(a) as being obvious over each of Badylak WO 98/25637 and Badylak US Patent 6,793,939 (national stage entry of PCT/US97/22727).**

It is noted the applied **patent** reference (US 6,793,939) has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2). Please note the WIPO publication is prior art under 35 USC 102(b) and cannot be overcome in such a manner.

In each reference Badylak disclose methods of inducing endogenous tissue formation at a site in need thereof by administering a graft composition comprising liver basement membrane in an amount effective to induce the repair of the liver tissue at the site of administration. Badylak disclose the graft composition can be used as part of a cell culture composition, having eukaryotic cells cultured thereupon. Specifically hepatocytes are amongst the cell types disclosed as being capable of growth thereupon (See WO 98/25637 Pg 12/ See USP '939 col. 8, ln 30-67); thus Badylak discloses a composition comprising the liver basement membrane and hepatocytes. Badylak disclose the graft composition can be administered as a multilayered composition formed from two or more layers of liver basement membrane (See WO 98/25637 Pgs 8-9/ See USP '939 col. 6, ln 13-64). The thickness of individual layers/sheets would be routinely optimized to suit the intended implantation site's needs (size and shape). Badylak further state the basement membrane can be provided in various forms, including a fluidized liquid

(which can also be considered a gel) or powder form (See WO 98/25637 Pg. 4-5/ See USP '939 col. 3, ln 45-col. 4, ln 11).

While Badylak state the graft composition can be administered to any endogenous tissue site in need of repair, he does not specifically disclose the liver as an implantation site. However, at the time the invention was made the need for a method of repair and/or regenerating liver tissue was well recognized, and thus the artisan of ordinary skill would have good reason to pursue treatment of the liver via the general method disclosed by Badylak. There would be a reasonable expectation that treatment of damaged liver would be successfully accomplished by the method of Badylak because the graft composition of Badylak contains basement membrane derived from liver tissue and Badylak suggests the material would support hepatocyte growth (See WO/ 98/25637 Pg. 12/ USP' 939, col. 8, ln 55-65). It is submitted that hepatocyte growth would achieve regeneration of liver tissue, which reads on repair of liver tissue. Therefore, it would have been obvious to the person of ordinary skill in the art to try to specifically repair liver tissue as the endogenous tissue site for repair by providing the liver basement membrane composition of Badylak with, or without, exogenous hepatocytes seeded thereupon, with a reasonable expectation that the composition would be suitable for use in liver tissue repair because such was a known option with a recognized need, and such a method would be within the technical grasp of the artisan. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d

887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 1-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,793,939.** Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets are directed to inducing formation of tissue in a subject in need thereof by implanting the same graft composition. The difference between the patented claims and the instant claims is that the patented claims are generic to repair of any endogenous tissue type, whereas the instant claims are specifically to repair of liver tissue. However, at the time the invention was made the need for a method of repair and/or regenerating liver tissue was well recognized, and thus the artisan of ordinary skill would have good reason to pursue treatment of the liver via the general method disclosed by Badylak. There would be a reasonable expectation that treatment of damaged liver would be successfully accomplished by the method of Badylak because the graft composition of Badylak contains basement membrane derived from liver tissue and Badylak suggests the material would support hepatocyte growth (See Badylak, col. 8, ln 55-65). Therefore, it would have been obvious to the person of ordinary skill in the art to try to specifically repair liver tissue as the endogenous tissue site for repair a reasonable expectation that the composition would be suitable for use in liver tissue repair because such was a known option with a recognized need, and such a method would be within the technical grasp of the artisan.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford Jr/
Primary Examiner, Art Unit 1651